REMARKS

Claims

Claims 1-7, 9, 11, and 50, are pending in the application.

Claim 1 is amended to specifically recite the stringent hybridization conditions at which a nucleic acid molecule hybridizes to a molecule consisting of the nucleic acid of SEQ ID NO:1 and is therefore encompassed by the present invention. Support for this amendment can be found throughout the application and at least on page 11, lines 10-14.

Claim 1 is further amended to recite that the nucleic acids of the invention encode a "polypeptide that binds a tyrosine kinase and downregulates its expression" instead of a "polypeptide that binds a tyrosine kinase and regulates its expression." Support for this amendment can be found throughout the application and at least on page 9, lines 12-30, and the Examples.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1-7, 9, 11, and 50 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner maintains that the claims contain "subject matter which was not described in the specification in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states that the specification, and more specifically page 8, line 27 - page 9, line 14, "merely asserts the invention," and that "said assertion is insufficient to support the claims to a nucleic acid which encodes a specific polypeptide with specific properties including *in vivo* activities."

Claim 1, as amended herewith, specifically recites that the nucleic acids of the invention encode a "polypeptide that binds a tyrosine kinase and downregulates its expression." Support for this amendment can be found throughout the application and at least on page 6, lines 17-26, on page 9, lines 12-30, and the Examples. More specifically, Example 6 describes the Applicants' observation that a cbl-SL polypeptide facilitates the downregulation of EGFR (a tyrosine kinase receptor) (see also Figure 8).

The Examiner further states that in paper No. 13 (Applicants' previous response), "Applicant further provides a short discource on the epidermal growth factor receptor and includes a number of references regarding said receptor's function," and that "said references can not provide additional support for the invention [sic] because the rejections are based on insufficient guidance regarding how to make and use the polypeptides encoded by the claimed nucleic acids."

Respectfully, Applicants disagree. Applicants provided said references to show how important the regulation of tyrosine kinase expression is in the field of cancer. Applicants teach cbl-SL nucleic acids and polypeptides, and that cbl-SL polypeptides bind and downregulate tyrosine kinases. Applicants provide sufficient guidance to one of ordinary skill in the art on how to make and regarding how to make and use the cbl-SL polypeptides encoded by the claimed nucleic acids of the present invention.

The Examiner maintains that the specification fails to provide sufficient evidence to establish that any cbl-SL protein is expressed.

Applicants provided in paper No. 13 (Applicants' previous response) evidence (by reciting the specific support from the specification) on why Applicants teach of an expressed cbl-SL protein (contrary to the Examiner's assertion). Respectfully, the Examiner has not provided any evidence in support of his assertion.

To re-iterate, Applicants teach that (i) a cbl-SL mRNA is expressed in specific tissues and cell lines (see at least Figures 1 and 2, and Example 2 on page 44), and (ii) a native cbl-SL polypeptide of ~ 50kd is recognized by a cbl-SL specific antisera (raised against an immunogenic peptide sequence encoded by a nucleic acid of Claim 1) (see at least Figures 4A and 4B, and Example 3). Applicants were able to show that a native (endogenous) cbl-SL polypeptide exists, and it is different from the cbl and cbl-b polypeptides of the prior art.

The Examiner maintains that "no *in vivo* biological activity is established for the naturally expressed protein or any of the claimed variants or fragments thereof," "particularly in consideration of the fact that the specification provides no *in vivo* data or examples."

Applicants teach, and argued above, of a specific cbl-SL polypeptide utility (i.e., "downregulation of tyrosine kinase expression"). According to M.P.E.P. 2164.02 and the "Training Materials For Examining Patent Applications With Respect To 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications," "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed"; "an example may be 'working' or 'prophetic'." Applicants describe a working example for one of many cbl-SL polypeptide uses (see e.g., Example 6). It is true that this is an *in vitro* observation. However, M.P.E.P. 2164.02 also describes (under CORRELATION: *IN VITRO/IN VIVO*) that "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or

claimed method invention." Applicants believe that "downregulation of tyrosine kinase expression" is both disclosed (see above) and/or claimed (see amended Claim 1).

In view of the foregoing amendments and arguments, Applicants respectfully request that the foregoing rejections of claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of Claims Under 35 U.S.C. §112, second paragraph

Claims 1-7, 9, 11, and 50, stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner maintains that the term "stringent conditions" is indefinite. Respectfully, Applicants disagree for the reasons stated at least in paper No. 13 (Applicants' previous response) , but in order to expedite prosecution of the present application Applicants have amended Claim 1 to specifically recite the stringent hybridization conditions at which a nucleic acid molecule hybridizes to a molecule consisting of the nucleic acid of SEQ ID NO:1 and is therefore encompassed by the present invention.

In view of the foregoing amendments and arguments, Applicants respectfully request that the foregoing rejections of claims under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejections of Claims Under 35 U.S.C. §112, first paragraph: New Grounds

Claims 1-3, and 50 are rejected under 35 U.S.C. §112, first paragraph. According to the Examiner, " the specification does not contain a written description of the claimed invention (i.e., no description for the term "regulates"), however, the Examiner finds support for "inhibits" or "downregulates."

Claim 1, as amended herewith, specifically recites that the nucleic acids of the invention encode a "polypeptide that binds a tyrosine kinase and downregulates its expression," thus rendering the "New Ground" rejection of claims under 35 U.S.C. §112, first paragraph, moot.

SUMMARY

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' representative would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Extension 286).

Respectfully submitted,

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MARKED-UP CLAIM

1 (Twice Amended). An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid molecule which hybridizes [under stringent conditions] at 65°C in hybridization buffer consisting essentially of 3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA, to a molecule consisting of the nucleic acid of SEQ ID NO:1 and which codes for a polypeptide that binds a tyrosine kinase and downregulates its expression,

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complements of (a) or (b).